09/923,637

Your SELECT statement is:
s cannabinoid(w)receptor? and cox?

Items	File
6	5: Biosis Previews(R)_1969-2002/Nov W3
6	34: SciSearch(R) Cited Ref Sci_1990-2002/Nov W4
3	71: ELSEVIER BIOBASE_1994-2002/Nov W3
5	73: EMBASE_1974-2002/Nov W3
1	91: MANTIS(TM)_1880-2002/Oct
1	135: NewsRx Weekly Reports_1995-2002/Nov W3
1	149: TGG Health&Wellness DB(SM)_1976-2002/Nov W2
6	155: MEDLINE(R)_1966-2002/Nov W3
4	159: Cancerlit_1975-2002/Oct
1	164: Allied & Complementary Medicine_1984-2002/Nov
1	266: FEDRIP_2002/Sep
2	399: CA SEARCH(R)_1967-2002/UD=13721
2	442: AMA Journals_1982-2002/Dec B2

SYSTEM:OS - DIALOG OneSearch
File 5:Biosis Previews(R) 1969-2002/Nov W3
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***File 5: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 155:MEDLINE(R) 1966-2002/Nov W3
***File 155: For updating information please see Help News155. Alert** feature enhanced with customized scheduling. See HELP ALERT.

Set	Items	Description
S1	12	CANNABINOID(W)RECEPTOR? AND COX?
S2	6	RD (unique items **2/9/3** **(Item 3 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

13082351 BIOSIS NO.: 200100289500
Effects of cannabinoids on LPS-stimulated inflammatory mediator release from macrophages: Involvement of eicosanoids.
AUTHOR: Chang Ying-Hsin; Lee Sho Tone; Lin Wan-Wan(a)
AUTHOR ADDRESS: (a)Department of Pharmacology, College of Medicine, National Taiwan University, Taipei: wwl@ha.mc.ntu.edu.tw**Taiwan
JOURNAL: Journal of Cellular Biochemistry 81 (4):p715-723 15 March-2 April, 2001
MEDIUM: print
ISSN: 0730-2312
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: DELTA9-Tetrahydrocannabinol (DELTA9-THC) is the major psychoactive component of marijuana and elicits pharmacological actions via **cannabinoid receptors** . Anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG) are endogenous ligands for **cannabinoid receptors** , which because of their structural similarities to arachidonic acid (AA), AEA, and 2-AG could serve as substrates for lipoxygenases and cyclooxygenases (**COXs**) that metabolize polyunsaturated fatty acids to potent bioactive molecules. In this study, we have compared the effects of DELTA9-THC, AEA, 2-AG, and another cannabinoid agonist, indomethacin morpholinylamide (IMMA), on lipopolysaccharide (LPS)-induced NO, IL-6, and PGE2 release from J774 macrophages. DELTA9-THC, IMMA, and AEA diminish LPS-induced NO and IL-6 production in a concentration-dependent manner. 2-AG inhibits the production of IL-6 but slightly increases iNOS-dependent NO production. DELTA9-THC and IMMA also inhibit LPS-induced PGE2 production and **COX** -2 induction, while AEA and 2-AG have no effects. These discrepant results of 2-AG on iNOS and **COX** -2 induction might be due to its bioactive metabolites, AA and PGE2, whose incubation cause the potentiation of both iNOS and **COX** -2 induction. On the contrary, the AEA metabolite, PGE2-ethanolamide, influences neither the LPS-induced NO nor IL-6 production. Taken together, direct

cannabinoid receptor activation leads to anti-inflammatory action via inhibition of macrophage function. The endogenous cannabinoid, 2-AG, also serves as a substrate for **COX** -catalyzing PGE2 production, which in turn modulates the action of CB2.

REGISTRY NUMBERS: 94421-68-8: ANANDAMIDE; 329900-75-6: CYCLOOXYGENASE-2; 10102-43-9: NITRIC OXIDE; 363-24-6: PROSTAGLANDIN E-2

2/9/6 (Item 6 from file: 5)

11289851 BIOSIS NO.: 199800071183

An update on eicosanoids and inhibitors of cyclooxygenase enzyme systems.

AUTHOR: Sharma Sangeeta; Sharma S C(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol. Therapeutics, Trinity Coll., Dublin 2** Ireland

JOURNAL: Indian Journal of Experimental Biology 35 (10):p1025-1031 Oct., 1997
ISSN: 0019-5189
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: There are 3 main enzymatic pathways for synthesis of eicosanoids from arachidonic acid, however, some compounds are also formed non-enzymatically. Among the enzymatic pathways, cyclooxygenase (**COX**) also known as prostaglandin synthase (PGHS), generates endoperoxides (PGG/H). These are converted into prostaglandins (PGs) and thromboxanes (TXs). The second pathway involves lipooxygenase (LOX) group of enzymes to provide hydroperoxyeicosatetraenoic acid (HpETEs) which in turn can be converted into leukotrienes (LTs), hepoxilins(HXs), trioxilins and lipoxins (LXs). The third pathway involves cytochrome P-450 which catalyses the formation of a number of monohydroxy fatty acids (hydroxyeicostetraenoic acids or HETEs) dihydroxy fatty acids (dihydroxyeicostetrienoic acids or DiHETrEs) and epoxyeicosatrienoic acids (EpETrEs: formerly called EETs) . This system also provides leukotoxins. The non-enzymatic pathway leads to the formation of isoprostanes by free radical catalysed peroxidation of arachidonic acid. In addition, brain cells also convert arachidonic acid into arachidonylethanolamide (anandarmide) which have the ability to bind to **cannabinoid receptors** . Most of these eicosanoids are either biologically active or are converted into metabolites which have biological activities. Cyclooxygenase is now known to exist in two separate isoforms which are called **COX** -1 and **COX** -2. While both isoforms catalyse the same reactions, the former is a constitutive enzyme and its activity is not markedly changed once the cell is fully grown. The later isoform is however inducible and its activity is several fold increased following the exposure of body cells to a number of stimuli and its contribution in the process of inflammation is now well documented. It is now believed that eicosanoids produced by **COX** -1 activity are essential for the physiological (house keeping) functions while those produced by **COX** -2 lead to various pathological changes in body tissues. Older nonsteroidal antiflammatory drugs like aspirin and indomethacin are non selective inhibitors of **COX** activity and therefore, in addition to inhibiting **COX** -2 activity, inhibit the formation of eicosanoids by **COX** -1. The later are required for normal house keeping functions such as secretion of mucus for protection of gastrointestinal mucosa, maintenance of renal function and control of haemostasis. Use of older non-selective NSAIDs has been associated with a number of gastrointestinal, renal and other side effects. Recently drugs such as nimesulide and meloxicam with selective action on **COX** -2 have been discovered and introduced into medicine. Evidence available so far has indicated the low incidence of side effects with these drugs. While being useful for various arthritic and other conditions, it is unlikely that these drugs will replace aspirin for the cardiovascular disease.

REGISTRY NUMBERS: 39391-18-9: CYCLOOXYGENASE; 506-32-1: ARACHIDONIC ACID; 9055-65-6: PROSTAGLANDIN SYNTHASE; 66719-58-2: THROMBOXANE; 9029-60-1Q: LIPOXYGENASE; 63551-74-6Q: LIPOXYGENASE; 9035-51-2: CYTOCHROME P450

09/923,637

Your SELECT statement is:
s (cox(w)2 or cox2)and 6(w)keto(w)prostaglandin?

Items	File
64	5: Biosis Previews(R)_1969-2002/Nov W2
37	34: SciSearch(R) Cited Ref Sci_1990-2002/Nov W3
30	71: ELSEVIER BIOBASE_1994-2002/Nov W2
35	73: EMBASE_1974-2002/Nov W2
1	98: General Sci Abs/Full-Text_1984-2002/Oct
16	144: Pascal_1973-2002/Nov W2
3	149: TGG Health&Wellness DB(SM)_1976-2002/Nov W2
39	155: MEDLINE(R)_1966-2002/Nov W2
19	156: ToxFile_1965-2002/Oct W4
10	159: Cancerlit_1975-2002/Oct
3	172: EMBASE Alert_2002/Nov W2
2	442: AMA Journals_1982-2002/Dec B2
1	444: New England Journal of Med._1985-2002/Nov W3

13 files have one or more items; file list includes 27 files.
SYSTEM:OS - DIALOG OneSearch
File 5:Biosis Previews(R) 1969-2002/Nov W2
(c) 2002 BIOSIS
***File 5: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 155:MEDLINE(R) 1966-2002/Nov W2
***File 155: For updating information please see Help News155. Alert** feature enhanced with customized scheduling. See HELP ALERT.
File 159:Cancerlit 1975-2002/Oct
(c) format only 2002 Dialog Corporation

Set	Items	Description
S1	10738	COX(W)2 OR COX2
S2	113	S1 AND 6(W)KETO(W)PROSTAGLANDIN?
S3	97	S2 NOT PY=>2002
S4	61	RD (unique items)
S5	0	S4 AND 2(W)ARACHIDONYLGLYCEROL
S6	22	S4 AND ARACHID?

6/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13444271 BIOSIS NO.: 200200073092
Sodium salicylate inhibits prostaglandin formation without affecting the induction of cyclooxygenase-2 by bacterial lipopolysaccharide in vivo.
AUTHOR: Giuliano Francesco; Mitchell Jane A; Warner Timothy D(a)
AUTHOR ADDRESS: (a)Department of Cardiac, Vascular and Inflammation Research, The William Harvey Research Institute, Barts and the London, Charterhouse Square, London, EC1M 6BQ**UK E-Mail: t.d.warner@mds.qmw.ac.uk
JOURNAL: Journal of Pharmacology and Experimental Therapeutics 299 (3):p 894-900 December, 2001
MEDIUM: print
ISSN: 0022-3565
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mechanisms underlying the anti-inflammatory properties of salicylate are not well understood. In particular, while salicylate inhibits prostaglandin production in vivo it only weakly inhibits cyclooxygenase (COX)-1 or -2 activity in vitro. Thus, it has often been suggested that in vivo salicylate may inhibit the expression rather than the activity of COX, particularly **COX - 2** . Using a model of acute **COX - 2** expression in the rat, we show that salicylate inhibits **COX - 2** activity in vivo without affecting **COX - 2** expression. In anesthetized rats LPS (6 mg kg-1, i.p.) increased the expression of **COX - 2** as evidenced by increased circulating levels of **6 - keto - prostaglandin** F1alpha (6-keto-PGF1alpha, a stable breakdown product of PGI2), greatly exaggerated formation of 6-keto-PGF1alpha following **arachidonic** acid

(AA) challenge (3 mg kg-1, i.v.), and increased expression of **COX - 2** , but not COX-1, protein. Diclofenac (3 mg kg-1, i.p.) or the **COX - 2** selective agent diisopropyl fluorophosphate (10 mg kg-1, i.p.) decreased the LPS-induced increase in circulating 6-keto-PGF1alpha and the exaggerated 6-keto-PGF1alpha production following AA challenge. Sodium salicylate (20 or 120 mg kg-1, i.p.) (administered either 1 h prior, or once per day for 3 days prior, to LPS injection) reduced only the LPS-induced increase in circulating 6-keto-PGF1alpha, but not the exaggerated 6-keto-PGF1alpha production following AA challenge or the expression of **COX - 2** . Thus, salicylate inhibits LPS-induced **COX - 2** activity in a manner that is overcome by provision of excess substrate and independent of effects on **COX - 2** expression. In conclusion, our results exclude mechanisms other than direct enzyme inhibition as responsible for the anti-COX effects of salicylate.

REGISTRY NUMBERS: 329900-75-6: CYCLOOXYGENASE-2; 54-21-7: SODIUM SALICYLATE

DESCRIPTORS:

MAJOR CONCEPTS: Immune System (Chemical Coordination and Homeostasis); Pharmacology

BIOSYSTEMATIC NAMES: Enterobacteriaceae--Facultatively Anaerobic Gram-Negative Rods, Eubacteria, Bacteria, Microorganisms; Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGANISMS: Escherichia coli (Enterobacteriaceae)--serotype O127:B8; Wistar rat (Muridae)--male

BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Animals; Bacteria; Chordates; Eubacteria; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

CHEMICALS & BIOCHEMICALS: **6 - keto - prostaglandin** F-1-alpha--formation; cyclooxygenase-2--activity, expression, inhibition; lipopolysaccharide; sodium salicylate--antiinflammatory-drug, enzyme inhibitor-drug, pharmacodynamics

6/9/2 (Item 2 from file: 5)

13250329 BIOSIS NO.: 200100457478

The effect of a selective cyclooxygenase-2 inhibitor in extended liver resection with ischemia in dogs.

AUTHOR: Takeyoshi Izumi(a); Sunose Yutaka(a); Iwazaki Shigeru(a); Tsutsumi Hirofumi(a); Aiba Masaaki(a); Kasahara Mureo(a); Ohwada Susumu(a); Matsumoto Koshi; Morishita Yasuo(a)

AUTHOR ADDRESS: (a)Second Department of Surgery, Gunma University School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma, 371-8511**Japan

JOURNAL: Journal of Surgical Research 100 (1):p25-31 September, 2001

MEDIUM: print

ISSN: 0022-4804

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Background. Pringle's procedure is commonly used during liver surgery, and it sometimes causes liver failure. Metabolites of **arachidonic** acid, which are converted by cyclooxygenase (Cox), are involved in ischemia-reperfusion injury. This study evaluated the effects of FK 3311, which selectively inhibits **Cox - 2** , on ischemia-reperfusion injury during liver resection in dogs. Materials and methods. The animals were divided into four groups and subjected to 60 min of warm ischemia by partial inflow occlusion. The FK-treated groups (FK0.2: 0.2 mg/kg, FK1: 1 mg/kg, FK3: 3mg/kg) received FK3311, and the control group received vehicle. Following reperfusion, the nonischemic lobes were resected and remnant liver function was evaluated. Results. Tissue blood flow and serum glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and lactate dehydrogenase were significantly better in the FK1 and FK3 groups, especially FK1, than in the control group. Thromboxane B2 was significantly lower in the FK1 and FK3 groups than in the control group. The level of **6 - keto - prostaglandin** F1alpha was significantly lower in the FK3 group and relatively unchanged in the FK1 group. Histological damage was milder in the FK1 group. There were significantly fewer polymorphonuclear neutrophils in the FK1 group than in the control group.

Conclusions. FK3311 ameliorates the ischemia-reperfusion injury caused by Pringle's procedure during extensive liver resection. This agent may be clinically useful in extended liver surgery involving vascular isolation.

6/9/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12696259 BIOSIS NO.: 200000449761
Cyclooxygenase-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning in conscious rabbits.
AUTHOR: Shinmura Ken; Tang Xian-Liang; Wang Yang; Xuan Yu-Ting; Liu Si-Qi; Takano Hitoshi; Bhatnagar Aruni; Bolli Roberto(a)
AUTHOR ADDRESS: (a)Experimental Research Laboratory, Division of Cardiology, University of Louisville, and Jewish Hospital Heart and Lung Institute, Louisville, KY, 40292**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 97 (18):p10197-10202 August 29, 2000
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We examined the role of cyclooxygenase-2 (**COX - 2**) in the late phase of ischemic preconditioning (PC). A total of 176 conscious rabbits were used. Ischemic PC (six cycles of 4-min coronary occlusions/4-min reperfusions) resulted in a rapid increase in myocardial **COX - 2** mRNA levels (+231 +- 64% at 1 h; RNase protection assay) followed 24 h later by an increase in **COX - 2** protein expression (+216 +- 79%; Western blotting) and in the myocardial content of prostaglandin (PG)E2 and 6-keto-PGF1alpha (+250 +- 85% and +259 +- 107%, respectively; enzyme immunoassay). Administration of two unrelated **COX - 2** selective inhibitors (NS-398 and celecoxib) 24 h after ischemic PC abolished the ischemic PC-induced increase in tissue levels of PGE2 and 6-keto-PGF1alpha. The same doses of NS-398 and celecoxib, given 24 h after ischemic PC, completely blocked the cardioprotective effects of late PC against both myocardial stunning and myocardial infarction, indicating that **COX - 2** activity is necessary for this phenomenon to occur. Neither NS-398 nor celecoxib lowered PGE2 or 6-keto-PGF1alpha levels in the nonischemic region of preconditioned rabbits, indicating that constitutive COX-1 activity was unaffected. Taken together, these results demonstrate that, in conscious rabbits, up-regulation of **COX - 2** plays an essential role in the cardioprotection afforded by the late phase of ischemic PC. Therefore, this study identifies **COX - 2** as a cardioprotective protein. The analysis of **arachidonic** acid metabolites strongly points to PGE2 and/or PGI2 as the likely effectors of **COX - 2** -dependent protection. The recognition that **COX - 2** mediates the antistunning and antiinfarct effects of late PC impels a reassessment of current views regarding this enzyme, which is generally regarded as detrimental.

6/9/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12524519 BIOSIS NO.: 200000278021
The induction of cyclooxygenase-2 in IL-1beta-treated endothelial cells is inhibited by prostaglandin E2 through cAMP.
AUTHOR: Akarasereenont Pravit; Techatrisak Kitirat; Chotewuttakorn Sirikul; Thaworn Athiwat
AUTHOR ADDRESS: (a)Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Prannok Rd, Bangkok, 10700**Thailand
JOURNAL: Mediators of Inflammation 8 (6):p287-294 1999
MEDIUM: print.
ISSN: 0962-9351
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: PROSTAGLANDINS (PGs) have numerous cardiovascular and inflammatory effects. Cyclooxygenase (COX), which exists as COX-1 and **COX - 2** isoforms, is the first enzyme in the pathway in which **arachidonic** acid is converted to PGs. Prostaglandin E2 (PGE2) exerts a variety of biological activities for the maintenance of local homeostasis in the body. Elucidation of PGE2 involvement in the signalling molecules such as COX could lead to potential therapeutic interventions. Here, we have investigated the effects of PGE2 on the induction of **COX - 2** in human umbilical vein endothelial cells (HUVEC) treated with interleukin-1beta (IL-1beta 1 ng/ml). COX activity was measured by the production of 6-keto-PGF1alpha, PGE2, PGF2alpha and thromboxane B2 (TXB2) in the presence of exogenous **arachidonic** acids (10 muM for 10 min) using enzyme immunoassay (EIA). COX-1 and **COX - 2** protein was measured by immunoblotting using specific antibody. Untreated HUVEC contained only COX-1 protein while IL-1beta treated HUVEC contained COX-1 and **COX - 2** protein. PGE2 (3 muM for 24 h) did not affect on COX activity and protein in untreated HUVEC. Interestingly, PGE2 (3 muM for 24 h) can inhibit **COX - 2** protein, but not COX-1 protein, expressed in HUVEC treated with IL-1beta. This inhibition was reversed by coincubation with forskolin (100 muM). The increased COX activity in HUVEC treated with IL-1beta was also inhibited by PGE2 (0.03, 0.3 and 3 muM for 24 h) in a dose-dependent manner. Similarly, forskolin (10, 50 or 100 muM) can also reverse the inhibition of PGE2 on increased COX activity in IL-1beta treated HUVEC. The results suggested that (i) PGE2 can initiate negative feedback regulation in the induction of **COX - 2** elicited by IL-1beta in endothelial cells, (ii) the inhibition of PGE2 on **COX - 2** protein and activity in IL-1beta treated HUVEC is mediated by cAMP and (iii) the therapeutic use of PGE2 in the condition which **COX - 2** has been involved may have different roles.

6/9/3 (Item 3 from file: 5)

12696259 BIOSIS NO.: 200000449761

Cyclooxygenase-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning in conscious rabbits.

AUTHOR: Shinmura Ken; Tang Xian-Liang; Wang Yang; Xuan Yu-Ting; Liu Si-Qi; Takano Hitoshi; Bhatnagar Aruni; Bolli Roberto(a)
AUTHOR ADDRESS: (a)Experimental Research Laboratory, Division of Cardiology, University of Louisville, and Jewish Hospital Heart and Lung Institute, Louisville, KY, 40292**USA

JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 97 (18):p10197-10202 August 29, 2000
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We examined the role of cyclooxygenase-2 (**COX - 2**) in the late phase of ischemic preconditioning (PC). A total of 176 conscious rabbits were used. Ischemic PC (six cycles of 4-min coronary occlusions/4-min reperfusions) resulted in a rapid increase in myocardial **COX - 2** mRNA levels (+231 +- 64% at 1 h; RNase protection assay) followed 24 h later by an increase in **COX - 2** protein expression (+216 +- 79%; Western blotting) and in the myocardial content of prostaglandin (PG)E2 and 6-keto-PGF1alpha (+250 +- 85% and +259 +- 107%, respectively; enzyme immunoassay). Administration of two unrelated **COX - 2** selective inhibitors (NS-398 and celecoxib) 24 h after ischemic PC abolished the ischemic PC-induced increase in tissue levels of PGE2 and 6-keto-PGF1alpha. The same doses of NS-398 and celecoxib, given 24 h after ischemic PC, completely blocked the cardioprotective effects of late PC against both myocardial stunning and myocardial infarction, indicating that **COX - 2** activity is necessary for this phenomenon to occur. Neither NS-398 nor celecoxib lowered PGE2 or 6-keto-PGF1alpha levels in the nonischemic region of preconditioned rabbits, indicating that constitutive COX-1 activity was unaffected. Taken together, these

results demonstrate that, in conscious rabbits, up-regulation of **COX - 2** plays an essential role in the cardioprotection afforded by the late phase of ischemic PC. Therefore, this study identifies **COX - 2** as a cardioprotective protein. The analysis of **arachidonic** acid metabolites strongly points to PGE2 and/or PGI2 as the likely effectors of **COX - 2** -dependent protection. The recognition that **COX - 2** mediates the antistunning and antiinfarct effects of late PC impels a reassessment of current views regarding this enzyme, which is generally regarded as detrimental.

6/9/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12109853 BIOSIS NO.: 199900404702
A771726, the active metabolite of leflunomide, directly inhibits the activity of cyclo-oxygenase-2 in vitro and in vivo in a substrate-sensitive manner.
AUTHOR: Hamilton Lorna C; Vojnovic Ivana; Warner Timothy D(a)
AUTHOR ADDRESS: (a)Vascular Inflammation, Medical College, William Harvey Research Institute, Charterhouse Square, **UK
JOURNAL: British Journal of Pharmacology 127 (4):p1589-1596 Aug., 1999
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: 1 The immunosuppressive and anti-inflammatory drug leflunomide has several sites of action, although its precise mode of action is unknown. 2 Here we show in vitro and in vivo that leflunomide and/or its active metabolite A771726, inhibit the activity of cyclo-oxygenase (COX) at doses below those that affect protein expression. 3 In J774.2 macrophages treated with endotoxin for 24 h to induce **COX - 2** and iNOS, leflunomide and A771726 inhibited more potently the accumulation of PGE2 (A771726, IC50 3.5 mug ml-1) than of NO2 (A771726, IC50 380 mug ml-1). At high concentrations (>300 mug ml-1) A771726 also exhibited the expression of **COX - 2** and iNOS proteins. 4 In A549 cells treated for 24 h with interleukin-1beta, to induce **COX - 2** , A771726 potently inhibited PGE2 synthesis (IC50 0.13 mug ml-1). In the same cells, A771726 was notably less active (IC50, 52 mug ml-1) at inhibiting the formation of PGE2 stimulated by exposure to 30 muM **arachidonic** acid. 5 In a human whole blood assay, measuring the accumulation of TxB2 in response to calcium ionophore as a measure of COX-1 activity and in response to incubation with bacterial endotoxin as a measure of **COX - 2** activity, leflunomide inhibited COX-1 and **COX - 2** with IC50 values of 31 and 185 mug ml-1; for A771726 the corresponding values were 40 and 69 mug ml-1. 6 Pre-treatment of rats with leflunomide or A771726 (10 mg kg-1, i.p.) inhibited the plasma accumulation of 6-keto-PGF1alpha but not NO2/NO3 following infusion of endotoxin. Injection of a bolus of **arachidonic** acid following 6 h infusion of endotoxin caused a marked acute rise in plasma 6-keto-PGF1alpha which was inhibited only by higher doses of A771726 (50 mg kg-1, i.p.). 7 In conclusion, leflunomide via A771726 can directly inhibit the activity of COX, an effect that appears blunted both by increases in substrate supply and possibly by plasma binding. Only at much higher drug levels does leflunomide and/or A771726 inhibit the induction of **COX - 2** or iNOS proteins.

6/9/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11696168 BIOSIS NO.: 199800477899
Interactions between inducible isoforms of nitric oxide synthase and cyclo-oxygenase in vivo: Investigations using the selective inhibitors, 1400W and celecoxib.
AUTHOR: Hamilton Lorna C; Warner Timothy D(a)
AUTHOR ADDRESS: (a)Vasc. Inflammation, William Harvey Res. Inst., St. Bartholomew's, Charterhouse Square, London EC**UK
JOURNAL: British Journal of Pharmacology 125 (2):p335-340 Sept., 1998

ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1. Exposure of tissues to endotoxin (LPS) and/or cytokines leads to the induction of both inducible nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (**COX - 2**). It has previously been reported that there is 'cross-talk' between these two systems. However, such previous studies have been limited by the availability of highly selective inhibitors. Here we have investigated the interactions between iNOS and **COX - 2** in vivo using 1400W, an iNOS-selective inhibitor, and celecoxib, a **COX - 2** -selective inhibitor. 2. Infusion of LPS to rats for 6 h caused a time-dependent increase in the plasma concentrations of **6 keto - prostaglandin** F1alpha (6 keto-PGF1alpha) and nitrite/nitrate (NO2/NO3), consistent with the induction of iNOS and **COX - 2** . Bolus injection of **arachidonic** acid (AA) at t = 6 h resulted in a further increase of circulating levels of 6 keto-PGF1alpha in LPS-treated animals. 3. Treatment of rats with 1400W or the non-selective NOS inhibitor NG-monomethyl-L-arginine (L-NMMA) inhibited the increase in plasma NO2/NO3 but were both without effect on the plasma concentration of 6 keto-PGF1alpha before or after AA. 4. Treatment with the non-steroidal anti-inflammatory drugs (NSAIDs), A771726 or diclofenac, or with celecoxib significantly reduced the increase in circulating 6 keto-PGF1alpha caused by LPS, and the large increase in 6 keto-PGF1alpha following injection of AA. None of the COX inhibitors affected the increase in plasma NO2/NO3. Dexamethasone, however, significantly inhibited both the increase in 6 keto-PGF1alpha and the increase in NO2/NO3. 5. In conclusion, the use of selective inhibitors does not support the concept of cross talk in vivo between iNOS and **COX - 2** .

6/9/12 (Item 12 from file: 5)

11344353 BIOSIS NO.: 199800125685
Selective inhibition of cyclooxygenase-2 by NS-398 in endotoxin shock rats in vivo.
AUTHOR: Futaki N(a); Takahashi S; Kitagawa T; Yamakawa Y; Tanaka M; Higuchi S
AUTHOR ADDRESS: (a)Pharmaceutical Res. Labs., Taisho Pharm. Co. Ltd., 1-403 Yoshino-cho, Ohmiya-shi, Saitama 330**Japan
JOURNAL: Inflammation Research 46 (12):p496-502 Dec., 1997
ISSN: 1023-3830
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective and Design: The role of cyclooxygenase (**COX**)- **2** was examined using a rat endotoxin shock model and the potency and selectivity of NS-398, a **COX - 2** selective inhibitor in vitro, for **COX - 2** activity was examined in vivo. Material: Male Wistar rats (weighing 140-180 g) were used. Methods: Lipopolysaccharide (LPS, 1 mg/kg, i.v.) was administered to rats (LPS-treated rats) and expression of COX-1 mRNA and **COX - 2** mRNA in the aorta and peripheral blood leukocytes was examined by RT-PCR. COX activity was assessed by measuring the plasma **6 - keto prostaglandin** (PG) F1alpha, PGE2 and thromboxane (TX) B2 30 s after administration of **arachidonic** acid (AA, 3 mg/kg, i.v.). NS-398 (0.3-100 mg/kg, p.o.) or indomethacin (0.3-3 mg/kg, p.o.) was administered 1 h before the AA injection. Results: **COX - 2** mRNA was detectable in the aorta and peripheral blood leukocytes at least from 3 to 9 h after the LPS injection but not in non-LPS-treated rats. Plasma 6-keto PGF1alpha, PGE2 and TXB2 levels after AA injection into LPS-treated rats were significantly enhanced compared to findings in non-LPS-treated rats. NS-398 showed significant inhibition of the increase in PGs in LPS-treated rats, the ED50 values being 0.35 mg/kg for 6-keto PGF1alpha, 1.5 mg/kg for PGE2 and < 0.3 mg/kg for TXB2. NS-398 even at 100 mg/kg did not significantly suppress the increased PGs levels in non-LPS-treated rats. In contrast, indomethacin significantly inhibited plasma PGs levels after AA injection into LPS-treated rats and

non-LPS-treated rats. The ED50 values in LPS-treated rats, determined by 6-keto PGF1alpha, PGE2 and TXB2 production, were 1.0, 1.3 and 2.3 mg/kg and those in non-LPS-treated rats were 0.42, 0.24 and 0.93 mg/kg, respectively. Conclusions: In a rat endotoxin shock model, expression of **COX - 2** plays a role in an increase in COX activity. NS-398 showed preferential inhibitory effects on **COX - 2** activity in vivo. This approach is useful to directly analyze the inhibitory activity of NSAIDs for COX-1 and **COX - 2** in vivo.

6/9/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11335847 BIOSIS NO.: 199800117179
Phospholipase A|2 metabolites regulate inducible nitric oxide synthase in myocytes.
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JOURNAL: Hypertension (Dallas) 31 (1 PART 2):p218-224 Jan., 1998
ISSN: 0194-911X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

order (2)

ABSTRACT: The proinflammatory cytokine interleukin-1beta (IL) stimulates inducible nitric oxide synthase (iNOS) mRNA, protein, and nitric oxide (NO) production in neonatal ventricular myocytes (NVM). In other types of cells, IL also activates phospholipase A2 (PLA2), which liberates **arachidonic** acid for the pathways involved in eicosanoid production, and induces the cyclooxygenase-2 (**COX - 2**) isoform, which increases prostanoid production. Since NO has been shown to directly stimulate COX activity and the resulting prostanoids to modulate IL induction of iNOS, we questioned whether PLA2 and/or COX products are involved in IL regulation of iNOS and NO production in NVM. We first found that IL induced **COX - 2** mRNA and protein, resulting in apprxeq200-fold and 15-fold increases-in PGE2 and 6-keto-PGF1alpha, (the stable metabolite of PGI2), respectively. IL-stimulated prostanoid production was inhibited by the **COX - 2** -specific inhibitor NS-398, as well as the nonspecific COX inhibitor indomethacin (INDO). We next studied the involvement of the PLA2 inhibitor ONO-RS-082 (ONO) and the COX inhibitor INDO in IL regulation of iNOS. Pretreatment with ONO blocked IL-stimulated NO production and iNOS protein, suggesting that PLA2 products are involved in regulation of iNOS synthesis. Unlike ONO, the COX inhibitor INDO had little effect on IL-stimulated NO. In addition to the COX pathway, **arachidonic** acid (AA) is also metabolized by the lipoxygenase (LO) pathway. The LO inhibitor nordihydroguaiaretic acid (NDGA) decreased IL-stimulated NO and iNOS synthesis. These data suggest that: (1) IL upregulates **COX - 2** expression and prostanoid production in NVM; and (2) AA metabolites other than COX products, possibly products of the LO pathway, are involved in IL regulation of iNOS.

6/9/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11277097 BIOSIS NO.: 199800058429
Induction of COX - 2 **in vivo leads to greatly increased production of 6-keto-PGF1alpha following administration of exogenous** arachidonic **acid or bradykinin.**
AUTHOR: Hamilton Lorna C; Mitchell Jane A; Warner Timothy D
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JOURNAL: British Journal of Pharmacology 122 (PROC. SUPPL.):p22P Oct., 1997
CONFERENCE/MEETING: Proceedings of the British Pharmacological Society Meeting Bristol, England, UK July 23-25, 1997
SPONSOR: British Pharmacological Society
ISSN: 0007-1188
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 506-32-1: **ARACHIDONIC** ACID; 58-82-2: BRADYKININ;

order (3)

58962-34-8: **6 - KETO - PROSTAGLANDIN** F 1 ALPHA; 9001-84-7: PHOSPHOLIPASE A-2; 125978-95-2: NITRIC OXIDE SYNTHASE

6/9/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11190484 BIOSIS NO.: 199799811629
Cyclooxygenase-2 unlike cyclooxygenase-1 is highly expressed in ovine embryos during the implantation period.
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JOURNAL: Biology of Reproduction 57 (5):p1032-1040 1997
ISSN: 0006-3363
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In this study we investigated expression of the two isoforms of the prostaglandin-forming enzyme, cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (**Cox - 2**), in sheep embryos. Using Western blot and immunohistochemical analyses, we demonstrated that **Cox - 2** was highly expressed in embryos from Day 8 to Day 17 of development whereas Cox-1 was undetectable during this time. The expression of **Cox - 2** was developmentally regulated. It was maximal between Days 14 and 16. There was a 30-fold increase in **Cox - 2** content per protein extract between Day 10 and Dar-14, corresponding to a 50 000-fold increase in the whole embryo. The expression of **Cox - 2** declined after Day 16 to become undetectable by Day 25 of pregnancy. **Cox - 2** was localized in the trophoblastic cells and was not detected in the inner cell mass. The (3H) **arachidonic** acid metabolites synthesized by **Cox - 2** -rich conceptuses were analyzed by HPLC after short-term embryo culture. Day 14 conceptuses released mainly cyclooxygenase metabolites and to a lesser extent lipoxygenase derivatives. Cyclooxygenase products were **6 - keto - prostaglandin** (PGF)-1alpha 18.2% (+- 4.2), thromboxane-B, 22.51% (+- 15.9), PGF-2alpha 21% (+- 11), PGE, 14.5% (+- 7.4), and PGD, 2.7% (+- 2.6). Taken together, these results suggest an important role for the Cox-2dependent cyclooxygenase metabolites during embryo development.

6/9/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10858364 BIOSIS NO.: 199799479509
Induction of cyclo-oxygenase-2 by cytokines in human cultured airway smooth muscle cells: Novel inflammatory role of this cell type.
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JOURNAL: British Journal of Pharmacology 120 (5):p910-916 1997
ISSN: 0007-1188
RECORD TYPE: Abstract
LANGUAGE: English

order (4)

ABSTRACT: 1. Cyclo-oxygenase (COX) is the enzyme that converts **arachidonic** acid to prostaglandin H-2 (PGH-2) which can then be further metabolized to prostanoids which modulate various airway functions. COX exists in at least two isoforms. COX-1 is expressed constitutively, whereas **COX - 2** is expressed in response to pro-inflammatory stimuli. Prostanoids are produced under physiological and pathophysiological conditions by many cell types in the lung. However, the regulation of the different COX isoforms in human airway smooth muscle (HASM) cells has not yet been determined. 2. COX-1 and **COX - 2** protein were measured by Western blot analysis with specific antibodies for COX-1 and **COX - 2** . **COX - 2** mRNA levels were assessed by Northern blot analysis by use of a **COX - 2** cDNA probe. COX activity was determined by measuring conversion of either endogenous or exogenous **arachidonic** acid to three metabolites, PGE-2, thromboxane B-2 or 6-ketoPGF-1alpha by radioimmunoassay. 3. Under control

culture conditions HASM cells expressed COX-1, but not **COX - 2** , protein. However, a mixture of cytokines (interleukin-1-beta (IL-1-beta), tumour necrosis factor alpha (TNF-alpha) and interferon gamma (IFN-gamma) each at 10 ng ml-1) induced **COX - 2** mRNA expression, which was maximal at 12 h and inhibited by dexamethasone (1 mu-M; added 30 min before the cytokines). Furthermore, **COX - 2** protein was detected 24 h after the cytokine treatment and the expression of this protein was also inhibited by dexamethasone (1 mu-M) and cyclohexamide (10 mu-g ml-1; added 30 min before the cytokines). 4. Untreated HASM cells released low or undetectable amounts of all COX metabolites measured over a 24 h period. Incubation of the cells with the cytokine mixture (IL-1-beta, TNF-alpha, IFN-gamma each at 10 ng ml-1 for 24 h) caused the accumulation of PGE-2 and 6-keto-PGF-1alpha. 5. In experiments where **COX - 2** metabolized endogenous stores of **arachidonic** acid, treatment of HASM cells with IL-1-beta in combination with TNF-alpha caused a similar release of PGE-2 to that when the three cytokines were given in combination. 6. In other experiments designed to measure **COX - 2** activity directly, cells were treated with cytokines for 24 h before fresh culture medium was added containing exogenous **arachidonic** acid (30 mu-M for 15 min) after which PGE-2 was measured. IL-1-beta and TNF-alpha increased **COX - 2** activity and an additional small increase was produced by the three cytokines in combination. 7. These findings suggest that the increased expression of **COX - 2** is intimately involved in the exaggerated release of prostanoids from HASM cells exposed to pro-inflammatory cytokines. These data indicate a role for airway smooth muscle cells, in addition to their contractile function, as inflammatory cells involved in the production of mediators which may contribute to the inflammatory response seen in diseases such as asthma.

6/9/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10793403 BIOSIS NO.: 199799414548
The inhibitory effects of mercaptoalkylguanidines on cyclooxygenase activity.
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JOURNAL: British Journal of Pharmacology 120 (3):p357-366 1997
ISSN: 0007-1188
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1. It has been proposed that in inflammatory conditions, in which both the inducible isoforms of nitric oxide synthase (iNOS) and cyclo-oxygenase (**COX - 2**) are induced, inhibition of NOS also results in inhibition of **arachidonic** acid metabolism. In the present study we have investigated whether mercaptoalkylguanidines, a novel class of selective iNOS inhibitors, may also influence the activity of cyclo-oxygenase (COX). Therefore, the effect of mercaptoethylguanidine (MEG) and related compounds on the activity of the constitutive (COX-1) and the inducible COX (**COX - 2**) was investigated in cells and in purified enzymes. Aminoguanidine, N-G-methyl-L-arginine (L-NMA) and N-G-nitro-L-arginine methyl ester (L-NAME) were also studied for comparative purposes. 2. Western blot analysis demonstrated a significant COX-1 activity in unstimulated J774 macrophages and in unstimulated human umbilical vein endothelial cells (HUVEC). Immunostimulation of the J774 macrophages by endotoxin (lipopolysaccharide of E. coli, LPS 10 mu-g ml-1) and interferon gamma (IFN-gamma, 100 u ml-1) for 6 h resulted in a significant induction of **COX - 2** , and a down-regulation of COX-1. No **COX - 2** immunoreactivity was detected in unstimutated HUVEC or unstimulated J774 cells. Therefore, in subsequent studies, the effect of mercaptoalkylguanidines on COX-1 activity was studied in HUVEC stimulated with **arachidonic** acid for 6 h, and in J774 cells stimulated with **arachidonic** acid for 30 min. The effect of mercaptoalkylguanidines on **COX - 2** activity was studied in immunostimulated J774 macrophages, both on prostaglandin production by endogenous sources, and on prostaglandin production in response to exogenous **arachidonic** acid stimulation. In

addition, the effect of mercaptoalkylguanidines on purified COX-1 and **COX - 2** activities was also studied. 3. In experiments designed to measure COX-1 activity in HUVEC, the cells were stimulated by **arachidonic** acid (15 mu-M) for 6 h. This treatment induced a significant production of 6-ketoprostaglandin F-1alpha (6-keto-PGF-1alpha, the stable metabolite of prostacyclin), while nitrite production was undetectable by the Griess reaction. MEG (1 mu-M to 3 mM) caused a dose-dependent inhibition of the accumulation of 6-keto-PGF-1alpha, with an IC-50 of 20 mu-M. However, aminoguanidine, L-NAME or L-NMA (up to 3 mM) did not affect the production of 6-keto-PGF-1alpha in this experimental system. In experiments designed to measure COX-1 activity in J774.2 macrophages, the cells were stimulated by **arachidonic** acid (15 mu-M) for 30 min; this also induced a significant production of 6-keto-PGF-1alpha and MEG (1 mu-M to 3 mM), aminoguanidine (at 1 and 3 mM), but neither L-NAME nor L-NMA inhibited the production of prostaglandins. 4. In experiments designed to measure prostaglandin production by **COX - 2** with endogenous **arachidonic** acid, J774.2 cells were immunostimulated for 6 h in the absence or presence of various inhibitors. In experiments designed to measure prostaglandin production by **COX - 2** with exogenous **arachidonic** acid, J774.2 cells were immunostimulated for 6 h, followed by a replacement of the culture medium with fresh medium containing **arachidonic** acid and various inhibitors. Both of these treatments induced a significant production of 6-keto-PGF-1alpha. Nitrite production, an indicator of NOS activity, was moderately increased after immunostimulation. MEG (1 mu-M to 3 mM) caused a dose-dependent inhibition of the accumulation of COX metabolites. Similar inhibition of LPS-stimulated 6-keto PGF-1alpha production was shown by other mercaptoalkylguanidines (such as N-methyl-mercaptoethylguanidine, N,N'-dimethyl-mercaptoethylguanidine, S-methyl-mercaptoethylguanidine and guanidino-ethyldisulphide), with IC-50 values ranging between 34-55 mu-M. However, aminoguanidine, L-NAME and LNMA (up to 3 mM) did not affect the production of prostaglandins. 5. In comparative experiments indomethacin, a non selective COX inhibitor, and NS-398, a selective **COX - 2** inhibitor, reduced (LPS) stimulated 6-keto-PGF-1alpha production in J774 macrophages in a dose-dependent manner without affecting nitrite release. Indomethacin, but not NS-398, inhibited 6-keto-PGF-1alpha production in the HUVECs. 6. The inhibitory effect of MEG was due to direct inhibition of the catalytic activity of COX as indicated in experiments with purified COX-1 and **COX - 2** . MEG dose-dependently inhibited the purified COX-1 and **COX - 2** activity with IC-50 values of 33 mu-M and 36 mu-M, respectively. Aminoguanidine (at the highest concentrations) inhibited the formation of COX-1 metabolites, without affecting **COX - 2** activity. High doses of L-NAME (3 mM) decreased COX-1 activity only, while L-NMA (up to 3 mM) had no effect on the activity of either enzyme. 7. These results suggest that MEG and related compounds are direct inhibitors of the constitutive and the inducible cyclo-oxygenases, in addition to their effects on the inducible NOS. The additional effect of mercaptoalkylguanidines on COX activity may contribute to the beneficial effects of these agents in inflammatory conditions where both iNOS and **COX - 2** are expressed.

6/9/19 (Item 19 from file: 5)

10379843 BIOSIS NO.: 199699000988

Cyclooxygenases-1 and -2 of endothelial cells utilize exogenous or endogenous arachidonic **acid for transcellular production of thromboxane.**

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JOURNAL: Journal of Biological Chemistry 271 (20):p12042-12048 1996
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The presence of prostaglandin (PG) H-2 in the supernatant of human umbilical vein endothelial cells (HUVEC) stimulated by thrombin

restores the capacity of aspirin-treated platelets to generate thromboxane (TX) B-2. Induction of cyclooxygenase-2 (**Cox - 2**) by interleukin (IL)-1-alpha or a phorbol ester increases this formation. HUVEC treated with aspirin lost their capacity to generate PGs but recovery occurred after 3- or 6-h induction of **Cox - 2** with phorbol ester or IL-1-alpha. Enzyme activity of the newly synthesized **Cox - 2** in aspirin-treated cells, evaluated after immunoprecipitation, was similar to untreated cells but after 18 h of cell stimulation only 5060% recovery of Cox-1 was observed. The use of SC58125, a selective **Cox - 2** inhibitor, confirmed these findings in intact cells. Cyclooxygenase activity was related to the amount of Cox proteins present in the cells, but after induction of **Cox - 2** , contribution of the latter to PG production was 6-8-fold that of Cox-1. Aspirin-treated or untreated cells were incubated in the absence or presence of SC58125 and stimulated by thrombin, the ionophore A23187, or exogenous **arachidonic** acid. The production of endogenous (6-keto-PGF-1alpha, PGE-2, PGF-2alpha) versus transcellular (TXB2) metabolites was independent of the inducer, the source of **arachidonic** acid and the Cox isozyme. However, in acetylsalicylic acid-treated cells, after 6-h stimulation with IL-1a, newly synthesized **Cox - 2** produced less TXB-2 than 6-ketoPGF-1alpha compared to untreated cells. At later times (gt 18 h), there was no metabolic difference between the cells. These studies suggest that in HUVEC, Cox compartmentalization occurring after short-term activation may selectively affect transcellular metabolism, but not constitutive production, of PGs.

6/9/20 (Item 20 from file: 5)

10183444 BIOSIS NO.: 199698638362

Activity of nimesulide on constitutive and inducible cyclooxygenases.

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JOURNAL: Arzneimittel-Forschung 45 (10):p1093-1095 1995
ISSN: 0004-4172
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English; German

ABSTRACT: Prostaglandins are pro-inflammatory but are gastroprotective. The gastric mucosa synthesizes prostaglandins mainly via constitutive cyclooxygenase (COX-1), whereas leucocytes have inducible enzyme (C)X-2). Nimesulide (CAS 51803-78-2) differentially inhibited prostanoid synthesis in these human tissues as well as with in vitro enzyme assays, and was less potent than indomethacin (CAS 53-86-1) on COX-1. Fresh human gastric mucosa was cut finely, washed and pre-incubated (100 mg in 1 ml phosphate buffered saline pH 7.4) with or without nimesulide or indometacin (0.1-100 mu-g/ml; 0 degree C; 30 min.). The fluid was replaced with fresh identical solution, incubated (37 degree C; 30 min) and the solution assayed. Isolated leucocytes from human peripheral blood were incubated (1-1.5 times 10-6, 2 ml Krebs' solution) with or without nimesulide or indometacin (0.1-100 mu-g/ml; 37 degree C; 1h), stimulated with lipopolysaccharide (5 mu-g/ml), further incubated for 24 h at 37 degree C and the medium assayed for the prostanoids PGE, TXB-2, 6-keto-PGF-1a and the leukotriene LTB-4 by radioimmunoassay (RIA). In vitro assays with COX-1 from ram seminal vesicles, or **COX - 2** from sheep placenta, were performed by pre-incubating the enzymes with vehicle alone (controls) or with drug for 5 min at 37 degree C. **Arachidonate** (10 mu-mol/l) was added and further incubated for 2 min at 37 degree C. Reactions were terminated and PGE determined by RIA. Both drugs caused concentration-related inhibitions of prostanoid accumulation in incubates of both tissues. Nimesulide reduced PGE accumulation more potently in incubates of stimulated leucocytes than of gastric mucosa. With gastric tissue, nimesulide was less potent than indometacin by approximately 6-22 fold (IC-50 for PGE, TXB-2, 6-keto-PGF-1alpha, respectively; 14.8 vs 2.5; 12.8 vs. 1.0; 31.1 vs 1.4 mu-mol/l; p lt 0.05 to 0.02). With the leucocytes, the concentrations of both drugs, particularly indomethacin

were not low enough to calculate the IC-50. With the in vitro assay, nimesulide (0.01 to 100 mu-mol/l) did not inhibit PGE formation by COX-1 but caused a concentration-related inhibition of PGE formation by **COX - 2** (4-60%). These results are consistent with the effective analgesic/anti-inflammatory activity of nimesulide coupled with better gastric tolerance compared to indometacin.

REGISTRY NUMBERS: 51803-78-2: NIMESULIDE; 39391-18-9D: CYCLOOXYGENASES; 54397-85-2: THROMBOXANE B-2; 58962-34-8: **6 - KETO PROSTAGLANDIN** F1-ALPHA

6/9/21 (Item 21 from file: 5)

10008199 BIOSIS NO.: 199598463117

Increased expression of inducible cyclooxygenase-2 in human endothelial cells by antiphospholipid antibodies.

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JOURNAL: Thrombosis and Haemostasis 74 (2):p770-777 1995
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effect of IgGs from 4 patients with antiphospholipid antibodies and elevated excretion of urinary 11-dehydro-thromboxane B-2 was evaluated on the production of prostacyclin by human endothelial cells in culture. After 6 h incubation, there was no change in **6 - keto - prostaglandin** F-1alpha in the supernatant. However patients' IgGs induced a marked increase in cyclooxygenase (Cox) activity compared to IgGs from 2 normal individuals or a commercial pool of I-Gs from normal donors, tested by adding exogenous **arachidonic** acid. Western blot analysis of the cellular Cox content using antibodies specific for the different forms of the enzymes revealed that patients' IgGs stimulated the synthesis of the newly described inducible **Cox - 2** without affecting the constitutive Cox-1. This effect was partially neutralized by preincubating the IgGs with phospholipids. The induction was dependent on the amount of IgGs; it was visible at 2 h and persisted up to 24 h. Analysis of mRNA levels showed a pattern of variation in good agreement with the results obtained for protein. The protein kinase inhibitor H-7 or long-term incubation of cells with PMA strongly reduced the induction. These results suggest that antiphospholipid antibodies may not prevent the potential of the vascular cells from generating higher amounts of prostacyclin in response to acute episodes of thrombosis.

6/9/22 (Item 22 from file: 5)

09815792 BIOSIS NO.: 199598270710

Co-induction of nitric oxide synthase and cyclo-oxygenase: Interactions between nitric oxide and prostanoids.

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JOURNAL: British Journal of Pharmacology 114 (7):p1335-1342 1995
ISSN: 0007-1188
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1. Lipopolysaccharide (LPS) co-induces nitric oxide synthase (iNOS) and cyclo-oxygenase (**COX - 2**) in J774.2 macrophages. Here we have used LPS-activated J774.2 macrophages to investigate the effects of exogenous or endogenous nitric oxide (NO) on **COX - 2** in both intact and broken cell preparations. NOS activity was assessed by measuring the

accumulation of nitrite using the Griess reaction. **COX - 2** activity was assessed by measuring the formation of **6 - keto - prostaglandin** F-1alpha (6-keto-PGF-1alpha) by radioimmunoassay. Western blot analysis was used to determine the expression of **COX - 2** protein. We have also investigated whether endogenous NO regulates the activity and/or expression of COX in vivo by measuring NOS and COX activity in the lung and kidney, as well as release of prostanoids from the perfused lung of normal and LPS-treated rats. 2. Incubation of cultured murine macrophages (J774.2 cells) with LPS (1 mu-g ml-1) for 24 h caused a time-dependent accumulation of nitrite and 6-keto-PGF-1alpha in the cell culture medium which was first significant after 6 h. The formation of both 6-keto-PGF-1alpha and nitrite elicited by LPS was inhibited by cycloheximide (1 mu-M) or dexamethasone (1 mu-M). Western blot analysis showed that J774.2 macrophages contained **COX - 2** protein after LPS administration, whereas untreated cells contained no **COX - 2** . 3. The accumulation of 6-keto-PGF-1alpha in the medium of LPS-activated J774.2 macrophages was concentration-dependently inhibited by chronic (24 h) exposure to sodium nitroprusside (SNP; 1-1000 mu-M). Sodium nitroprusside (1-1000 mu-M) also acutely (30 min) inhibited **COX - 2** activity in broken cell preparations of LPS-activated (12h) J774.2 macrophages, in a similar concentration-dependent manner. Addition of adrenaline (5 mm) and glutathione (0.1 mM) increased the activity of **COX - 2** in broken cell preparations. In the presence of these co-factors, SNP inhibited prostanoid production only at the highest concentration used (1 mM). When J774.2 cells were incubated in the presence of LPS (1 mu-g ml-1) and N-monomethyl-L-arginine (L-NMMA: 1 mM) for 12 h, SNP at the highest concentration used (1 mM) acutely (30 min) inhibited the activity of **COX - 2** in cell homogenates with co-factors. However, when J774.2 macrophages were incubated for 24 or 12 h with LPS (1 mu-g ml-1) and L-NMMA (1 mM), the addition of SNP (0.001-1000 mu-M) increased in a concentration-dependent manner the accumulation of 6-keto-PGF-1alpha in intact cells (measured at 24 h) and **COX - 2** activity in cell homogenates in the presence of co-factors (determined at 12 h). SNP (1 mM; together with LPS for 12 h) decreased the amount of **COX - 2** protein induced by LPS in J774.2 macrophages. 4. Indomethacin (30 mu-M) abolished the formation of 6-keto-PGF-1alpha by LPS-activated macrophages, but had no effect on the release of nitrite. Conversely, L-NMMA, at the highest concentrations used (1 and 10 mM), increased the release of 6-keto-PGF-1alpha, an effect which was reversed by excess L-arginine (3 mM) but not by D-arginine. Similarly, the decrease in nitrite formation caused by L-NMMA was partially reversed by L-arginine (3 mM), but not by D-arginine. L-NMMA (10 mM; together with LPS for 12 h) increased the amount of **COX - 2** protein induced by LPS in J774.2 macrophages. 5. In separate experiments, J774.2 macrophages were activated with LPS (1 mu-g ml-1), and L-NMMA (10 mM) was added for various times (0.5-24h) before the collection of medium at 24 h. L-NMMA enhanced the release of 6-keto-PGF-1alpha in a time-dependent manner, with the maximal enhancement seen when the NOS inhibitor was incubated with the cells for 24 h. 6. In experiments on male Wistar rats, we investigated the effect of L-NMMA on the release of prostanoids (6-keto-PGF-1alpha, prostaglandin E-2, thromboxane B-2) elicited by **arachidonic** acid (AA, 30 nmol) from ex vivo perfused kidneys and lungs. The release from the organs from normal and LPS-treated rats was unaffected by L-NMMA intraperitoneally (30 mg kg-1) for 6 h together with LPS (5 mg kg-1) or LPS vehicle. Similarly, acute (15 min) in vitro exposure to L-NMMA (1 mM) of the perfused organs from control and LPS-treated animals did not change the release of prostanoids elicited by AA (30 nmol). 7. These results show that LPS causes the induction of iNOS and **COX - 2** in J774.2 macrophages. The co-release of NO and PGI-2 induced by LPS is dependent on protein synthesis and occurs after a lag-time of 6-12 h. The formation of COX metabolites has no effect on NOS activity whereas NO inhibits both **COX - 2** activity and induction. These results demonstrate that NOS and COX can be co-induced in vitro and that under these conditions large amounts of NO inhibit the degree of COX expression and activity. In the absence of endogenous NO, lesser amounts of exogenous NO increase the activity of **COX - 2** . In those situations in vivo when the level of NO induction is relatively low, NO does not regulate the increased activity of COX.

REGISTRY NUMBERS: 125978-95-2: NITRIC OXIDE SYNTHASE; 39391-18-9:

CYCLO-OXYGENASE; 10102-43-9: NITRIC OXIDE; 35121-78-9: PROSTAGLANDIN I-2; 58962-34-8: **6 - KETO - PROSTAGLANDIN** F-1-ALPHA; 506-32-1: **ARACHIDONIC** ACID; 54397-85-2: THROMBOXANE B-2

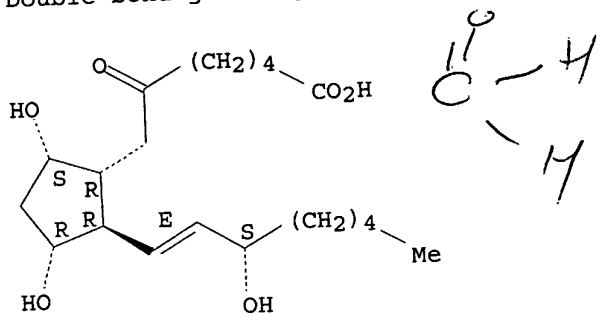
L1 ANSWER 1 OF 4431 CAPLUS COPYRIGHT 2002 ACS

IT **58962-34-8**, 6-KetoPGF1.alpha.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effects of celecoxib and diclofenac on blood pressure, renal function, and vasoactive prostanoids in healthy young and elderly subjects: effect on urinary eicosanoid excretion)

RN 58962-34-8 CAPLUS

CN Prost-13-en-1-oic acid, 9,11,15-trihydroxy-6-oxo-, (9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L1 ANSWER 1 OF 4431 CAPLUS COPYRIGHT 2002 ACS
AN 2002:721328 CAPLUS
DN 137:272957
TI Effects of celecoxib and diclofenac on blood pressure, renal function, and vasoactive prostanoids in young and elderly subjects
AU Dilger, Karin; Herrlinger, Charlotte; Peters, Joerg; Seyberth, Hannsjoerg W.; Schweer, Horst; Klotz, Ulrich
CS Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany
SO Journal of Clinical Pharmacology (2002), 42(9), 985-994
CODEN: JCPCBR; ISSN: 0091-2700
PB Sage Publications
DT Journal
LA English
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 1 OF 4431 CAPLUS COPYRIGHT 2002 ACS

AB Cyclooxygenase (COX) inhibitors are among the most widely used drugs, esp. in the elderly. It has been claimed that the new COX-2 inhibitors offer advantages in terms of drug safety. To test this hypothesis, the authors compared in a double-blind, randomized trial the effects of celecoxib (200 mg bid) and diclofenac (75 mg bid) on blood pressure and renal function in two groups (each n = 12) of young (mean age = 32 yr) and elderly (mean age = 68 yr) normotensive subjects. Changes from baseline in the 24-h blood pressure profiles, parameters of the renin-angiotensin-aldosterone system, inulin clearance, urinary marker proteins, and eicosanoid excretion were monitored during the treatment period of 2 wk. Comparison between celecoxib and diclofenac showed no significant difference in minor alterations of blood pressure. During daytime, there was a trend to elevation of mean arterial blood pressure (mmHg) by celecoxib in the elderly of 2.8 (95% confidence interval [CI] = -2.5 to 8.2) in comparison with the young subjects of -1.3 (95% CI = -3.7 to 1.0); there was also a trend to elevation of mean arterial blood pressure by diclofenac in the elderly of 4.1 (95% CI=-1.2 to 9.4) in comparison with the young subjects of 0.4 (95% CI=-2.4 to 3.2). In both populations, the authors found no significant drug effects on the parameters of the renin-angiotensin-aldosterone system, inulin clearance, and urinary marker proteins. As expected, diclofenac reduced excretion of all prostanoids, whereas celecoxib did not affect prodn. of TxB2 and its metabolites. Neither in young nor in elderly normotensive subjects were blood pressure and renal function significantly affected by a short-term treatment with std. doses of celecoxib and diclofenac. Therefore, normal aging appears not to represent a special risk factor in therapy with these two agents.

FILE 'CAPLUS' ENTERED AT 13:55:17 ON 18 NOV 2002
L1 0 S 2-ARACODONYLGLYCEROL
L2 27 S ARACHIDONYL GLYCEROL
L3 1 S L2 AND (COX-2 OR COX2)

```
s 2-aracodonylglycerol
      7520373 2
            0 ARACODONYLGLYCEROL
            0 2-ARACODONYLGLYCEROL
L1              (2(W)ARACODONYLGLYCEROL)

=> s arachidonyl glycerol
          662 ARACHIDONYL
       116079 GLYCEROL
         1187 GLYCEROLS
       116517 GLYCEROL
                (GLYCEROL OR GLYCEROLS)
L2          27 ARACHIDONYL GLYCEROL
                (ARACHIDONYL(W)GLYCEROL)

=> s l2 and (cox-2 or cox2)
        10073 COX
            2 COXES
        10075 COX
                (COX OR COXES)
      7520373 2
         4131 COX-2
                (COX(W)2)
         1588 COX2
L3          1 L2 AND (COX-2 OR COX2)

=> d l3 1

L3   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
AN   2001:789933  CAPLUS
DN   136:50128
TI   Functional characterization of cyclooxygenase-2 polymorphisms
AU   Fritsche, Ellen; Baek, Seung Joon; King, Lorraine M.; Zeldin, Darryl C.;
     Eling, Thomas E.; Bell, Douglas A.
CS   Laboratory of Computational Biology and Risk Analysis, National Institute
     of Environmental Health Sciences, Research Triangle Park, NC, USA
SO   Journal of Pharmacology and Experimental Therapeutics (2001), 299(2),
     468-476
     CODEN: JPETAB; ISSN: 0022-3565
PB   American Society for Pharmacology and Experimental Therapeutics
DT   Journal
LA   English
RE.CNT  39    THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d l3 1 ab

L3   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
AB   Cyclooxygenases (COX)-1 and -2 are the key enzymes in the conversion of
     arachidonic acid to prostaglandins. COX-2 appears to
     play an emerging role in inflammation and carcinogenesis. Nonsteroidal
     anti-inflammatory drugs (NSAIDs) are used for the treatment of numerous
     diseases and reduce the risk of developing colorectal cancer.
     Polymorphisms in the COX-2 gene could alter enzyme
     expression, function, and/or the response to NSAIDs. Therefore, they
     could modify individual risks for developing cancer and other diseases or
     the occurrence of side effects or sensitivity toward selective or
     nonselective COX inhibitors. We sequenced the COX-2
     gene of 72 individuals and identified rare polymorphisms in the promoter
     and the coding region. A COX-2 mol. model was used to
     locate the coding region polymorphisms relative to functional sites in the
     protein, and the COX-2 V511A polymorphism was very
     near to the active site. This variant protein was expressed, and function
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was evaluated, but no difference was detected in metab. of the COX -2 substrates, arachidonic acid, linoleic acid, and 2-**arachidonyl glycerol**, compared with the wild type. The Km values for arachidonic acid showed no differences between the **COX-2** wild type and V511A mutant. Inhibition with selective or nonselective COX inhibitors was essentially the same for the two enzymes. The absence of functionally important polymorphisms in the **COX-2** gene may suggest that there has been selective pressure against those single nucleotide polymorphisms because of the crit. role of this enzyme in maintenance of homeostasis.

Your SELECT statement is:
s pg(w)g and (cox2 or cox(w)2)

Items	File
2	5: Biosis Previews(R)_1969-2002/Nov W2
3	34: SciSearch(R) Cited Ref Sci_1990-2002/Nov W3
1	71: ELSEVIER BIOBASE_1994-2002/Nov W3
2	73: EMBASE_1974-2002/Nov W2
1	94: JICST-EPlus_1985-2002/Sep W3
1	144: Pascal_1973-2002/Nov W3
1	149: TGG Health&Wellness DB(SM)_1976-2002/Nov W2
2	155: MEDLINE(R)_1966-2002/Nov W2

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File 5:Biosis Previews(R) 1969-2002/Nov W2
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removal, customized scheduling. See HELP ALERT.
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***File 34: Alert feature enhanced for multiple files, duplicates**
removal, customized scheduling. See HELP ALERT.
File 155:MEDLINE(R) 1966-2002/Nov W2
***File 155: For updating information please see Help News155. Alert**
feature enhanced with customized scheduling. See HELP ALERT.

Set	Items	Description
S1	1735	PG(W)G?
S2	7	S1 AND (COX2 OR COX(W)2)
S3	4	RD (unique items)

L1 ANSWER 1 OF 17 MEDLINE
ACCESSION NUMBER: 2002672235 IN-PROCESS
DOCUMENT NUMBER: 22320028 PubMed ID: 12432915
TITLE: Recent developments in cyclooxygenase inhibition.
AUTHOR: **Marnett Lawr nce J**
CORPORATE SOURCE: Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN 37215, USA..
marnett@toxicology.mc.vanderbilt.edu
CONTRACT NUMBER: CA89450 (NCI)
GM15431 (NIGMS)
SOURCE: PROSTAGLANDINS AND OTHER LIPID MEDIATORS, (2002 Aug) 68-69 153-64.
Journal code: 9808648. ISSN: 1098-8823.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20021116
Last Updated on STN: 20021116

ABSTRACT:
Recent studies of the mechanism and selectivity of inhibition of cyclooxygenase enzymes are reviewed. The structural determinants of inhibition by the non-selective inhibitor, aspirin, and COX-2-selective diarylheterocycles are considered. Kinetic investigations indicate that the time-dependence of binding and inhibition of COX-1 and COX-2 by diarylheterocycles is more complex than originally postulated. The selectivity of inhibition is not determined by differences in the rates of association of the inhibitors with the two enzymes but rather by differences in the rates of dissociation. New strategies for the development of COX-2-selective inhibitors are highlighted.

L1 ANSWER 2 OF 17 MEDLINE
ACCESSION NUMBER: 2002423592 MEDLINE
DOCUMENT NUMBER: 22152966 PubMed ID: 12162745
TITLE: Kinetics of inhibition of leukocyte 12-lipoxygenase by the isoform-specific inhibitor 4-(2-oxapentadeca-4-yne)phenylpropanoic acid.

AUTHOR: Moody John S; **Marnett Lawrence J**
CORPORATE SOURCE: Department of Biochemistry, Vanderbilt-Ingram Comprehensive Cancer Center and Center in Molecular Toxicology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, USA.

CONTRACT NUMBER: CA47479 (NCI)
CA68485 (NCI)
ES00267 (NIEHS)
GM15431 (NIGMS)
SOURCE: BIOCHEMISTRY, (2002 Aug 13) 41 (32) 10297-303.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020816
Last Updated on STN: 20020904
Entered Medline: 20020903

ABSTRACT:
Lipoxygenases (LOXs) are a ubiquitous family of enzymes that catalyze the dioxygenation of polyunsaturated fatty acids. Their role in a diverse range of biological processes has prompted the development of a large number of lipoxygenase inhibitors of possible therapeutic and probative value. The isoform-selective inhibitor 4-(2-oxapentadeca-4-yne)phenylpropanoic acid (OPP) was previously shown to inhibit leukocyte-type 12-LOX by a novel mechanism in which it binds to both the ferrous and ferric forms of the enzyme. The current study provides a detailed kinetic model of this inhibition. Nonlinear regression analysis of OPP's inhibition of arachidonic acid dioxygenation indicated mixed inhibition toward the ferric form of 12-LOX with apparent K(I) values in the low micromolar range: 2.0 +/- 0.2 microM for the free enzyme and 4.5 +/- 0.7 microM for the substrate-bound form of the enzyme. Rapid kinetic techniques allowed OPP's inhibition of the activation of the enzyme from the ferrous to the ferric form to be investigated. Titration of ferrous 12-LOX with OPP indicated that it bound to the ferrous form with an apparent K(I) value of 70 +/- 20 nM, suggesting a significantly higher affinity for the ferrous form than for the ferric form of the enzyme. Investigation of the LOX inhibitors nordihydroguaiaretic acid, N-(4-chlorophenyl)-N-hydroxy-N'-(3-chlorophenyl)urea, BWA137C, and eicosatetraynoic acid revealed that eicosatetraynoic acid also inhibited the activation of 12-LOX. These results demonstrate that LOX inhibitors are capable of binding to multiple forms of LOXs with high affinity and suggest that inhibition of enzyme activation may be an unrecognized mechanism of inhibition of additional LOX inhibitors.

CONTROLLED TERM:
Check Tags: Animal; Support, U.S. Gov't, P.H.S.
5,8,11,14-Eicosatetraynoic Acid: CH, chemistry
*Arachidonate 12-Lipoxygenase: AI, antagonists & inhibitors
*Arachidonate 12-Lipoxygenase: CH, chemistry
Binding Sites
Binding, Competitive
*Enzyme Inhibitors: CH, chemistry
Isoenzymes: AI, antagonists & inhibitors
Isoenzymes: CH, chemistry
Kinetics
*Leukocytes: EN, enzymology
Linoleic Acids: AI, antagonists & inhibitors
Linoleic Acids: CH, chemistry
Lipid Peroxides: AI, antagonists & inhibitors

Lipid Peroxides: CH, chemistry
Oxidation-Reduction
Oxygen: AI, antagonists & inhibitors
Oxygen: CH, chemistry
*Phenylpropionates: CH, chemistry
Swine

CAS REGISTRY NO.: 1191-85-1 (5,8,11,14-Eicosatetraynoic Acid); 23017-93-8 (13-hydroperoxy-9,11-octadecadienoic acid); 7782-44-7 (Oxygen)

CHEMICAL NAME: 0 (4-(2-oxapentadeca-4-yne)phenylpropanoic acid); 0 (Enzyme Inhibitors); 0 (Isoenzymes); 0 (Linoleic Acids); 0 (Lipid Peroxides); 0 (Phenylpropionates); EC 1.13.11.31 (Arachidonate 12-Lipoxygenase)